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CENTRAL AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM (PHARMACOLOGICAL ASPECTS)[1,2]

By W. D. M. Paton

Royal College of Surgeons of England, London, England

Criteria for Chemical Transmission Across Synapses

The swing of the pendulum, by which the theory of chemical transmission has come to assume a dominant role in concepts of central transmission, has continued. The reviewer believes that the transmission process at central nervous synapses may indeed be in principle chemical, and that the role of electrotonic potentials imposed by one neurone on another may be that of modulating the effects of specific chemical substances. But viewed pharmacologically, the evidence now accepted for central chemical transmission is often weak, certainly weaker than that put forward many years ago to support the theory of chemical transmission at neuromuscular or ganglionic synapses, when it was not generally received. The evidence for the latter junctions was essentially as follows:—that the presynaptic neurone could (*a*) synthesize the transmitter and (*b*) release it in pharmacologically identifiable form; and that its action on the postsynaptic cell should (*c*) reproduce the specific events of normal transmission, and (*d*) be antagonized by competitive blocking agents. That there should exist (*e*) an enzyme destroying the transmitter is also important, although the significance of its presence in the presynaptic endings is less clear than when it is found (as at the motor endplate) in close association with the postsynaptic receptor site. For rigorous proof, none of this evidence can be dispensed with; its force lies in its conjunction. Thus the placenta contains acetylcholine; cobra venom and red cells are rich in cholinesterase; and acetylcholine and drugs like it can not only excite sensory and other nerve endings but be antagonized at these sites by d-tubocurarine or hexamethonium. But at none of these sites is a cholinergic synapse concerned. Enzyme inhibitors also lead to ambiguties. Eserine, for instance, inhibits both true and pseudocholinesterase, has some atropine-like action, and can paralyze transmission in nerve (331). The phosphorous antiesterases inhibit not only cholinesterase but proteolytic enzymes and aliesterases (235) and may well have a concealed anaesthetic potency (313). To obtain specific effects by the use of drugs, in short, demands as much care and pharmacological insight as the use of stimulating or recording electrodes demands of electrophysiological knowledge and experience. The most decisive evidence for chemical transmission, i.e., collection and identification of the

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[1] The survey of literature pertaining to this review was completed in June, 1957.

[2] In this chapter, subscript i or o denotes respectively intracellular or extracellular concentration of an ion.

transmitter after stimulating the pre-synaptic neurone, together with the demonstration that the transmitter applied artificially can produce the characteristic postsynaptic events, has not yet been obtained for any specific central synapse, although the work on the activation of the Renshaw cells, in conjunction with previous knowledge of chemical transmission at motor nerve endings, comes very close.

This review will be concerned chiefly with pharmacological aspects of synaptic transmission; but since pharmacological actions are being increasingly studied by electrophysiological methods, some of the work on bioelectric potentials which promises to be important for interpretation of chemical synaptic events will be discussed. Synaptic transmission at the motor endplate and at the electroplax are discussed by del Castillo & Katz (56) and by Grundfest (148) respectively. The Proceedings of the International Symposium on Curare and Curare-like Agents (178a) contain a useful account of current work on the motor endplate, including the studies by P. Waser, and C. Chagas and their collaborators on the fixation of radioactive curare preparations by endplate receptors. The symposium on Hormones, Brain Function and Behaviour (167a) includes a critical discussion on the role of 5-hydroxytryptamine in the central nervous system. The Herter lectures by Eccles (81) review much recent work including that from his own laboratory.

THE DISTRIBUTION OF COMPONENTS OF POSSIBLE TRANSMITTER MECHANISMS

Table I summarizes some of the available information as to the distribution of these components. The interpretation of such figures is not easy [see (110) for a discussion of some of the factors involved]. Burgen & Chipman (50a) also determined succinic dehydrogenase activity in a variety of nervous tissues, to obtain an estimate of the general metabolic activity of the tissues concerned. It is possible that a fairer idea of the significance of a given activity would be obtained from the ratio between that activity and the succinic dehydrogenase activity, as measuring roughly the content of transmitter component per unit metabolizing tissue. Certainly, if this is done, a somewhat different picture emerges.

Acetylcholine. Hebb & Silver (162) find that choline acetylase activity is limited by supply of acetyl-coenzyme A, especially with rapid rates of synthesis. Taking account of this, they have determined choline acetylase activity in the central nervous system, with results similar to those of Feldberg & Vogt (110), but obtaining much higher activity in active tissues (caudate nucleus and ventral roots can synthesize 10 to 15 mg. acetylcholine/gm. tissue/hr.) and more regular results. Their data have been used in Table I. Burgen *et al.* (49) examined the substrate specificity of the enzyme. Hebb & Smallman (163) have shown it to be concentrated in mitochondrial particles deposited at 12,000g., although the activity of the particles is low until they are treated with ether. In a sectioned nerve [Hebb & Waites, (164)] choline acetylase accumulates centrally, and falls distal to the point of section, indicating that, as with cholinesterase, the main cell body is the source of enzyme. In growing rabbits and guinea-pigs (161) the choline acetylase in cerebrum rises steadily to its adult value at 30 to 100 days, but cerebellar content (much lower in the adult) reaches an early maximum and then declines. Choline acetylase can be inhibited by hemicholiniums (216) but the drug appears to interfere with choline access to the enzyme rather than with the enzyme itself (130). Bose & Gupta (28) found that feeding rats paludrine, quinine, or mepacrine lowered acetycholine content of brain, heart and liver. The general picture of choline acetylase distribution is still compatible with Feldberg & Vogt's suggestion that cholinergic and noncholinergic neurones tend to alternate, and with the notion that the most primitive pathways (phylogenetically) are cholinergic. Cerebellar cortex, optic nerve, and dorsal roots remain outstandingly low in choline acetylase content, caudate, and ventral roots outstandingly high.

Histamine.—Histamine is known to occur in peripheral nerve and in the infundibular region, but brain and spinal cord contain little (see 92, 104, 182, 322). Feldberg & Greengaard (107) have shown it to be present in cat sciatic nerve freed of its perineurium, and for a part of it to be releasable from both sites. Murray & Paton (232) have made similar observations; maximum release possible fails to interfere with conduction of motor impulses. The fact that histamine content increases rather than decreases after nerve section has prompted the latter workers to compare histamine content with Schwann cell counts; the histamine content seems to be highest in those nerves with a high ratio of Schwann cells to axoplasm, and an increase in Schwann cells is known to occur after nerve section. It seems most likely at present that the histamine is associated with Schwann cytoplasm rather than with the axone. If this is true, it may apply to other substances too; and if some of the glia can be regarded as analogous to Schwann tissue (99) distribution of certain active substances may be a function of glial arrangement as much as of specific neurones. Sympathins have already been found in gliomas, as well as cholinesterase (47).

Sympathin.—The distribution of norepinephrine and epinephrine was established by Vogt's (317) classical study, demonstrating their localization (chiefly as norepinephrine) in those regions concerned with central autonomic representation. Monoamine oxidase occurs in the brain, especially in the hypothalamus and medulla (310), but doubts are accumulating as to whether this is the main enzyme concerned in sympathin destruction.

Hydroxytryptamine.—Paasonen & Vogt (243) using a test object (Spisula heart) insensitive to epinephrine and pituitary hormone, have verified the conclusion of Amin *et al.* (7) that autonomic ganglia and posterior pituitary are free of 5-hydroxytryptamine. Albrecht *et al.* (3) find that 5-hydroxytryptamine of mouse brain is lower in late afternoon than in the morning. The figures for 5-hydroxytryptamine distribution in Table I are taken from Amin *et al.* (7) and Paasonen & Vogt (243). Udenfriend & Bogdanski (310) give higher values obtained by a fluorimetric method, with similar regional varia-

TABLE I

Tissue	1 Acetyl-choline µg./gm.	2 Choline acetylase mg./gm. hr.	3 Q Mech.	4 Q Benz.	5 Substance P u./gm.	6 5-hydroxy-tryptamine µg./gm.	7 HTn. decarb-oxylase µg./gm./hr.	8 Mono-amine oxidase	9 Norepi-nephrine µg./gm.	10 Hist-amine µg./gm.	11 Succinic dehydro-genase
	Column										
Cortex	—	—	—	—	—	—	—	844	0.11	0	—
3 (somaesthetic)	2.8	—	150	—	—	—	—	—	0	—	—
4 (motor)	*4.5*	3	178	42	19	0.02	—	—	0.18	—	88
17 (visual)	2.2	1.3	107	—	7.3	0	—	—	0.04	—	—
51 (olfactory)	—	*3.7*	466	91	29	0.016	—	—	0.12	—	44
Hippocampus	—	—	—	—	15	0.045	—	—	—	—	—
Corpus Callosum	2.1	—	16	27	6	0	—	—	0.08	—	13
Olfactory bulb	1.3	1.2	197	—	6	0.05	—	—	—	—	—
Optic tract	—	—	86	76	—	—	—	—	—	—	—
Optic nerve	0.3	0	11	*222*	6	—	—	—	0.02	—	3
Caudate nucleus	2.7*	*13.3*	*3936*	*360*	46	0.10	0.6	—	0.06	0	134
Thalamus	3	3.1	409	161	13	0.02	—	886	—	0	90
Lateral nuc.	—	—	—	—	8.4	0?	—	—	0.08	—	—
Medial nuc.	—	—	—	—	11	0.07	—	—	0.24	—	—
Geniculates											
lateral	—	2.6	230	—	—	—	—	—	0.07	—	—
medial	—	*3.2*	316	—	—	—	—	—	0.13	—	—
Hypothalamus	1.8	2.0	323	*358*	*70*	*0.25*	0.45	3154	*1.03*	*1–30*	—
Superior colliculi	1.65	2.3	*932*	159	20	*0.13*	—	—	0.16	—	68
Inferior colliculi	—	1.4	364	184			—	—	0.11	—	80
Red nucleus	—	—	452	—	—	—	—	—	*0.26*	—	—
Pons	—	—	—	—	—	—	2.6	882	0.20	—	—
Medulla	1.6	—	—	—	25	0.03	2.6	1250	—	—	—
Pyramids	0.2	—	82	94	—	—	—	—	0.06	—	—
					460	*0.24*	0	—	*1.04*	—	—

Tissue	1 Acetyl-choline μg./gm.	2 Choline acetylase mg./gm. hr.	3 Q Mech.	4 Q Benz.	5 Substance P u./gm.	6 5-hydroxy-tryptamine μg./gm.	7 HTn decarb-oxylase μg./gm./hr.	8 Mono-amine oxidase	9 Norepi-nephrine μg./gm.	10 Hist-amine μg./gm.	11 Succinic dehydro-genase
Cerebellum	0.18	0.09	1075	24	2	0.01	0	970	0.07	0	100
Inf. ped.	—	—	295	—	41	0	—	—	—	—	—
Middle ped.	—	0.33	243	50			—	—	—	—	10
Sup. ped.	—	—	333	90			—	—	—	—	—
N. grac. & Cun.	—	—	477	—	*110*	*0.17*	0.11	—	0.11	—	—
Spinal cord	1.6	—	—	—	29	0	—	—	—	0	—
Grey matter	*3.0*	—	*611*	*218*	*68*	0.08	—	—	0.16	—	—
Dorsal column	0.05	—	36	27	—	—	—	—	—	—	7
Post. roots	0.04	<0.02	—	—	40	0	—	—	0.01	—	<2
Ant. roots	*15*	*11*	149	20	6	0	—	—	0.06	—	<2
Symp. ganglion	*30*	—	—	—	4–9	0	45	—	*6*	*c5*	—
References	215a	162	50a	50a	7,243	7,243	126	310	317	182, 322	50a

* Corpus striatum.

The table has been constructed from the available evidence for dog tissues. The columns show in turn (1.) Acetylcholine content, in μg./gm. fresh tissue: (2.) Chóline acetylase activity, in mg./acetylcholine synthesized/gm. wet wt./hour: (3.) Rate of hydrolysis of methacholine, in μl. CO_2 evolved/gm. wet wt./10 min., as an estimate of true cholinesterase activity: (4.) Rate of hydrolysis of benzoylcholine, in μl. CO_2 evolved/gm. wet wt./10 min., as an estimate of pseudo-cholinesterase activity: (5.) Substance P content, in units/gm. wet wt.: (6.) 5-hydroxytryptamine content, in μg./gm. wet weight: (7.) 5-hydroxytryptophan decarboxylase activity, in μg. 5-hydroxytryptamine formed /gm. tissue wet wt./hr.: (8.) Monoamine oxidase activity, in μg. 5-hydroxytryptamine destroyed/gm. homogenized tissue/hr.: (9.) Norepinephrine content, in μg./gm. wet wt.: (10.) Histamine content, in μg./gm. wet wt.: (11.) Succinic dehydrogenase activity as a percentage of activity of cerebellar hemispheres, which had an absolute activity of 167 μg. succinic acid dehydrogenated/gm. wet wt./hr.

In columns 1 to 6 and 9, the four highest values in each column are indicated by italicized figures.

tions. Gaddum & Giarman (126) have studied the distribution of 5-hydroxytryptaphan decarboxylase. It is widespread in the alimentary tract; the kidney is particularly rich (45 to 200 μg. 5-hydroxytryptamine formed/gm./hr.), but plasma is free of it. Sympathetic ganglia are very rich, and the cerebral peduncles, pons, medulla, hypothalamus, and caudate nucleus contain it. The substrate concentration/action curve is bell-shaped for the enzyme from nervous tissue. Curious anomalies exist, area postrema is rich in 5-hydroxytryptamine, low in enzyme; autonomic ganglia are free of 5-hydroxytryptamine but rich in enzyme; the caudate and hypothalamus contain both. Monoamine oxidase, which can destroy 5-hydroxytryptamine, is especially concentrated in hypothalamus, and to a less extent the medulla (310). In general the distribution of the 5-hydroxytryptamine system is not dissimilar from that of sympathin.

Substance P.—Paasonen & Vogt (243) agree with earlier work that hypothalamus and caudate contain large amounts. Area postrema may have considerably higher values than the ala cinerea, and the ala cinerea than the trigonum hypoglossi. P has also been found in fish intestine and brain (von Euler & Ostlund, 93); and Eliasson *et al.* (88) have failed to substantiate the suggestion that P from the intestine differs from that in brain. It is known to be present in retina (79). Substance P synthesis and metabolism have hardly been studied; although presumably normal pathways for peptide synthesis and breakdown are concerned. Umrath has speculated that P is the carrier for acetylcholine (in bound form) in cholinergic neurones, and for the sensory transmitter in dorsal roots (312). It is curious that the distribution of substance P is not unlike that of the 5-hydroxytryptamine system and of sympathin except for its concentration in dorsal roots and their central pathway. The area postrema may contain more substance P than does any other tissue.

The inhibitor substance of Florey (I).—This material (89, 112, 113) obtained by extraction of brain with boiling water, followed by dialysis, concentration and further purification, is assayed by its depressant action on the discharge of the crayfish stretch-receptor. It is distinguished from acetylcholine, substance P, histamine, sympathin, 5-hydroxytryptamine and ATP, and is identified as γ-amino-β-hydroxy-butryic acid. It is remarkable that Hayashi & Nagai (160), in a study of compounds of this type for anticonvulsant activity when applied to the cortex, selected this particular compound as being a possible central inhibitor. Hanawara (152) has studied retinal metabolism, and the effect of various amino acids. Florey & McLennan (112, 113) found that Florey's inhibitory substance (I) is not destroyed in blood, and that it does not occur in sympathetic ganglia, sciatic nerve, liver, spleen, or heart. It accumulates in fluid placed in a cup over the cortex of a cat, with dura opened. Knowledge about γ-aminobutyric acid and similar compounds is rapidly accumulating; a valuable critical survey is that of Elliott (88a).

Other substances.—Crossland & Mitchell (73) have obtained, from trichloracetic acid extracts of cerebellum at room temperature, a material which when injected into the carotid artery produces cerebellar activation. It is very stable at alkaline pH but can be destroyed by boiling with acid. Extracts of cerebellum also destroy it, but not if they are previously boiled. The active material is found in optic nerve and dorsal roots.

Ambache (5) has further characterized Irin, a substance extracted from iris and believed to mediate the prolonged pupillary constriction resulting from handling the trigeminal nerve. It is distinct from acetylcholine, histamine, 5-hydroxytryptamine, bradykinin and substance P. Its action is long-lasting, up to several hours. From partition experiments it appears to be an acid.

Vogt (318) has shown that *Darmstoff*, a smooth muscle stimulant, extractable from intestine, has the properties and chemical properties of a phosphatidic acetal. In an interesting paper he reviews the lipoid-soluble acids of natural occurrence, and suggests that such compounds might act as mobile cation-exchangers in cell-membranes. Sphingosine (114) (a base in sphingomyelin) has been found to have a significant, but irreversible, spasmolytic action on isolated intestine. It may be relevant that White & Sanson (325) find that injections of fatty acid anions can produce EEG spindling and the appearance of sleep.

Lissak & Endroczi (207), from watery extracts of nervous tissue, obtained a substance spasmolytic on the small intestine, and depressing cortical excitability and spinal reflexes; it protects mice against strychnine and eserine convulsions. It is dialyzable, but is broken down in aqueous solution. Kuriaki & Haraguchi (196) describe a lipoid soluble vasodilator in brain. Regional difference in content of glycerylphosphoryl choline (320) and of prophyrins (295) may also become important.

Comment.—Despite the undoubted importance attaching to any naturally occurring substance, none of the substances mentioned, save acetylcholine, commend themselves as transmitters for specific neural responses, because of their relatively prolonged action or their evident chemical stability. Central synaptic events are commonly both rapidly repetitive (firing rates up to 1000/sec. are described) and relatively transient in their course; only after prolonged repetitive stimulation do events with a time course of minutes occur, and these may well be due to ionic shifts associated with propagated activity in somata, dendrites, and axones rather than to transmitter accumulation. Transience of synaptic action is, in any case, necessary if inextricable blurring of successive signals is not to occur; and the results of prolonged transmitter action at the neuromuscular junction (54, 303, 304, 305) indicate that synaptic function might be radically disorganized if transmitters had other than a transient action. This is not a decisive argument, since the required transience of action might be achieved by release at point sources and diffusion away from them. But the weight of the argument is proportional to the significance attached, for instance, to cholinesterase. The reviewer suspects that the substances identified may bear the same sort of relation to undiscovered transmitters as choline does to acetylcholine. The appearance of pharmacologically active anions is of particular interest.

As mediators for diffuse responses, particularly of the reticular formation, sympathin, 5-hydroxytryptamine, substance P, offer themselves, in addition to any role acetylcholine may play. P is usually discussed in terms of transmission by the first sensory neurone; but apart from its presence there, the fact that, like 5-hydroxytryptamine and sympathin, it is concentrated in area postrema and hypothalamus, and (relatively) in medial rather than lateral thalamus, gives it almost an equally good (or bad) claim with these for a reticular function. Vogt's valuable critical discussion (317) of the possible function of cerebral sympathin is still relevant to the other possible transmitters.

Release of Transmitters

Transmitter substances.—Angelucci (8) has used the oxygen-perfused, Ringer-bathed, frog spinal cord preparation, from which flexor reflexes, inhibited by contralateral excitation, can be obtained. On stimulation, increases of acetylcholine output (in the presence of eserine), and of substances resembling 5-hydroxytryptamine and substance P, were obtained in small quantities. Unexpectedly, reserpine (which is known to mobilize 5-hydroxytryptamine from platelets, intestine, and brain) lowered the output of 5-hydroxytryptamine-like substance.

Acetylcholine output has been studied principally on peripheral structures. Emmelin & MacIntosh (90) have verified that acetylcholine output in ganglia or muscles perfused with blood is comparable with output from Locke-perfused tissues, and have discussed critically the nature of events in chemical transmission. Kostial & Vouk (193) find that for an excitation rate of 2/sec., acetylcholine output from a cat's perfused superior cervical ganglion is little reduced by cooling unless to 20°C. or lower. They suggest that Brown's (44) earlier observation that output fell to one-tenth between 39°C. and 20°C. was related to his more rapid stimulus rate (10/sec), with which the rate of acetylcholine resynthesis might have become limiting and caused a greater temperature senstivity. Studies on miniature endplate potentials have continued (30, 56a, 124a, 204). The externally recorded potential difference may exceed that recorded across the endplate membrane because of a concentration of current flow in the synaptic gap (56a). Such potentials have not been seen in autonomic ganglia (81) so that it is not established whether acetylcholine release is also quantal at interneuronal synapses, although it is hard to imagine that it is not.

Paton (252, 253) has shown that the output of acetylcholine by guinea pig ileum is considerably increased by coaxial stimulation, which elicits brief twitches, having the pharmacological properties of a response mediated by postganglionic cholinergic neurones (250). No other gut stimulant was released in significant amounts. Although it is known that histamine, 5-hydroxytryptamine and substance P are present in intestine, as in the brain stem, the nervous transmission of stimulant effects by the nerve network of the intestine appears to be wholly cholinergic.

Gillespie & Brown (135), in a study of sympathin output from spleen and gut, made the interesting observation that treatment with dibenamine increased the amount of norepinephrine recovered; they interpret this to mean that the receptors destroy as well as receive the transmitter. This situation contrasts with cholinergic synapses, at which receptors can be blocked without interfering with the amount of transmitter collected.

Accommodation to acetylcholine.—Conventional theories of drug action usually assume that the activity of a drug bears some relation to the occupation of receptor sites by the drug concerned, so that as the proportion of sites occupied reaches some equilibrium value the effect of the drug achieves a stable sustained peak. In fact, however, a sustained action by a drug is almost impossible to achieve. Drugs such as histamine, hydroxytryptamine, and Substance P, when applied to the small intestine, elicit a waning contraction and if a large dose is applied and subsequently washed out a desensitization to the drug is obtained which is often specific if the dose is carefully chosen. This type of phenomenon often comes under the heading of "tachyphylaxis" and forms the basis of the Barsoum-Gaddum desensitization method for identifying substances in the absence of a specific inhibitor. A similar accommodation to the stimulant drug at the motor endplate occurs with acetylcholine and drugs like it. It has been repeatedly recorded that the effect of acetylcholine or decamethonium at an endplate will produce during a particular administration a waning depolarization, and a smaller effect on subsequent administrations, even when apparent complete recovery of membrane potential has taken place between successive doses (54, 78, 101). A striking example of this is the observation by Thesleff (303, 304, 305) that in a frog sartorius exposed to acetylcholine the initial endplate depolarization (measured with internal electrodes) may with lapse of time entirely disappear. Krivoy & Wills (194) record a curious accommodation in isolated ganglia whereby acetylcholine produces a sustained depolarization but transmission returns (the exact converse of Thesleff's observation). Pascoe (246), however, found acetylcholine action to lessen with successive applications. Thesleff believes that acetylcholine can produce a competitive block comparable to that produced by d-tubocurarine. The muscle will certainly have lost appreciable quantities of potassium (189, 251) and other ion movements have probably occurred. But since the membrane conductance of the muscle in this state is still within normal limits, the defect must be in a failure by acetylcholine to produce permeability changes, rather than in a change of possible equilibrium potentials. A similar phenomenon has been found on the frog rectus abdominis muscle when its response to acetylcholine is studied, not by allowing it to contract against an isotonic lever, but by stretching the muscle to a constant length and finding the tension developed (254). Under these conditions the "active state" induced by the drug wanes with time, sometimes quite rapidly, and the muscle becomes eventually completely resistant to acetylcholine. Sensitivity is only slowly recovered after washing out. Since acetylcholine should be rapidly destroyed at the nerve-endings and could hardly be expected to persist, as, say, d-tubocurarine can, it seems more likely that acetylcholine induced some "refractoriness" of the receptors rather than that it exerts an ordinary curare-like action. A very interesting related clinical development is described by Churchill-Davidson & Richardson (59). After noting that the condition of a myasthenic patient deteriorated with activity, and that the effect of anticholinesterases was ultimately to make her worse after a temporary improvement, they concluded that the myasthenic motor endplate changed its response to acetylcholine, so that acetylcholine (or its products) came to curarise the endplate. Zaimis (335) on the basis of experiments with depolarizing drugs on the muscles of a variety of animals, put forward a similar proposal and Grob *et al.* (147) have made kindred observations. Churchill-Davidson and Richardson accordingly "rested" the endplates by curarising the patient for a period of eight days. The curare requirement was soon within normal limits. At the end of this period as the curare wore off the patient improved remarkably, and neostigmine had a dramatic effect, the patient becoming stronger than for a long time.

Although accommodation of central nervous structures to the action of stimulant drugs has been little studied, it may be of considerable importance in interpreting some of the results obtained. Any drug action, in which more than brief effects are obtained and in which the response changes, for instance, from stimulant to inhibitory, may involve such a process.

Mechanisms Involved in the Genesis of Bioelectric Potentials

Peripheral nerve.—Hodgkin & Keynes (168, 169) showed in 1955 that after prolonged stimulation of a squid axone, the process of sodium extrusion and potassium recovery were coupled, and were "active" in the sense of proceeding against electrochemical gradients and being paralyzed by metabolic inhibitors. As a result of their work on dinitrophenol-poisoned fibres, for which potassium flux ratios of 0.1 were obtained, they concluded that K^+ ions undergoing passive diffusion interacted as though they had to traverse, in single file, channels through the membrane accommodating about three ions. Subsequently (170) they have developed a refined method for injection inside axones; KCl so administstered had little effect, but NaCl led to a reduction of "overshoot" and a small rise in resting potential attributable to accelerated Na^+ extrusion. They were able to show that Na efflux is proportional to intracellular sodium, Na_i, although the constant of proportionality falls with time: the onset of accelerated efflux after NaCl injection was immediate. $MgCl_2$ and d-tubocurarine were inactive, but $CaCl_2$ abolished conduction and rendered the axoplasm fluid and opaque. The "toxicity" of intraaxonal calcium agrees with Keynes & Lewis' (185) conclusion that the concentration of Ca in squid axoplasm cannot be above 0.1–0.3 molar. The latter authors, with Gilbert & Fenn (134) suggest that calcium is actively extruded from the fibre. Frankenhaeuser (119) has further shown that reduction of extracellular calcium, Ca_o, to zero will paralyze conduction in frog myelinated nerve, although 0.01 mM is sufficient to maintain excitability.

Frankenhaeuser & Hodgkin (121), have shown that the external calcium profoundly influences Na and K exchanges; a fivefold reduction of Ca_o is equivalent (in its action in facilitating increase in sodium conductance, inactivation of the sodium-carrying system, and rise in K conductance) to a membrane depolarization of 10 to 15 mV.

Afterpotentials in peripheral nerve.—Brown & Holmes (45), and Ritchie & Straub (266, 267) have made a very interesting analysis of the afterpotentials following repetitive stimulation of mammalian C fibres (cervical sympathetic and hypogastric nerves). After such stimulation, the recorded spike and the size and duration of the afternegativity are increased and a large afterpositivity appears, as Gasser & Grundfest had earlier shown. The change in spike height is due, not to a change in absolute height, but to the spike "taking-off" from the afterpositivity, and to an increasing contribution to the recorded spike by the enhanced afternegativity, particularly if dispersion is increased by long conduction distances. The afternegativity appears only as the hyperpolarization develops. Brown & Holmes find that the phenomenon is prominent for all fibres conducting less than 1.1 m/sec, and believe it to be a property of nonmyelinated nerves. Analyzing the hyperpolarization, Ritchie & Straub found it to be delayed in high external potassium; reduced by low external potassium, by dinitrophenol and other metabolic inhibitors, by ouabain, and by substituting lithium for sodium; prolonged in sucrose or choline Na-deficient media; and independent of external chloride concentration. After metabolic inhibitors and lithium, post-tetanic depolarization replaces the normal hyperpolarization. Holmes (172) studying the post-tetanic enhancement of the action potential, obtained, on cat hypogastric nerve, similar results in some respects, but with a lower dose of DNP found it produced only a delay in time course of the enhancement. Ritchie & Straub propose that during excitation, a relatively large quantity of sodium enters the fibres, and potassium leaves (some of which diffuses away). During recovery sodium extrusion coupled to potassium influx lowers extracellular potassium, K_o, immediately outside the fibres faster than it can be replaced by diffusion from surrounding fluid; K_i/K_o thus temporarily rises above normal levels, leading to the hyperpolarization. The theory explains the phenomena described, and the fact that the hyperpolarization approaches but does not exceed the membrane potential recorded in K-free solution. The theory assumes a diffusion barrier round the nerve, and predicts that the hyperpolarization will develop in proportion to the surface-volume ratio of the fibre. Holmes (172), however, interprets his experiments in terms of a prolonged K conductance following the passage of a train of impulses.

Frankenhaeuser & Hodgkin (120) in a study of the effects of nerve impulses in squid axon also invoke a diffusion barrier. They noticed that the afterpositivity of the spike in a train dwindles as the train continues; this effect is larger with low K_o and is reduced by high K_o and by rise of temperature (which reduces the K output per shock). A diffusion barrier, spaced about 300 Å from the membrane (it need contribute only slightly to the total membrane resistance), behind which K^+ may accumulate, explains the results, together with certain voltage-clamp observations; and Hodgkin and Huxley's theory of the nerve impulse can be extended to include the negative after-potential. Frankenhaeuser and Hodgkin found, in electron-microphotographs obtained by B. B. Geren & F. O. Schmitt, a barrier of the position and nature postulated.

Shaw *et al.* (283), having failed to obtain the expected correlation between K_i and Na_i and the resting or action potential respectively, criticize the current theory of membrane potential. Katz (183) criticizes Easton's (80) suggestion that the effect of nerve stimulation on the muscle action potential recorded at the endplate is due to current from adjacent fibres, and shows that if the membrane potential is raised so that the impaled fibre will not conduct an impulse from the endplate, the endplate potential recorded is of normal shape, despite activity in adjacent fibres.

Neurones of the central nervous system.—Eccles (81) has reviewed the recent experiments in his laboratory which have shed so much light on neuronal physiology. In the resting state, the neurone has a membrane potential of 70 mV, about 20 mV less than the K^+ equilibrium potential, implying normal resting K^+ intrusion. When activated antidromically, the full spike response is slowed in both rising and falling phases by injection of Na^+ ion (which raises Na_i and lowers K_i), consistent with the Hodgkin-Huxley theory for propagated action in nerve. During synaptic activation the equilibrium potential approaches zero; the depolarizing excitatory postsynaptic potential (e.p.s.p.) is largely proportional to the membrane potential; and the injection of various ions had no specific effect; all these results indicate a "short-circuit" resulting from synaptic action. During inhibitory responses the hyperpolarizing inhibitory postsynaptic potential (i.p.s.p.) was found to have an equilibrium potential about -80 mV, and responses to injected ions were compatible with a specific increase of permeability to small ions (K and Cl). The positive afterpotential following antidromic excitation had an equilibrium potential of -90mV and other properties corresponding to a persising K permeability. Four specific permeability changes are thus envisaged, such that the membrane potential is dominated by the movement down electrochemical gradients of sodium (rising phase of spike), potassium (falling phase and afterpositivity), all small ions (inhibitory postsynaptic potential) or all ions (excitatory postsynaptic potential).

Fatt's (102) analysis of potentials round a single activated motoneurone proposes a reidentification of the components of potentials recorded. The response elicited had (after a small initial positivity) two phases: a negative deflection culminating in a plateau, from which arose a further negative spike. The first plateau was identified as soma response because (*a*) it was maximal nearest where penetration of the neurone occurred, (*b*) it resembled soma intracellular records, (*c*) it was a large potential requiring a large source, (*d*) it did not propagate. Given this conclusion, the spike which follows the plateau and may fail to appear in blocked neurone, could hardly be other than dendritic. This was confirmed by finding evidence of propagation of the spike at about 1 m./sec. The threshold for soma activation was about 10 mV, and its height 30 mV; dendritic response was elicited at 30 mV, giving a spike of 80 mV. Fatt concludes that the NM (nonmedulated part of axone) response of Brock *et al.* (36) (which Eccles has now rechristened IS for initial segment) is in fact somatic; that the SD (soma-dendrite) response is dendritic; and that it is the soma-dendrite junction rather than the axon-hillock that is a point of easy block.

This conclusion was supplemented by orthodromic studies (103); potential steps can be identified (particularly clearly by electrically differentiating the record) in synaptic and intracellular spikes, corresponding to the successive activation of the soma and of the dendrites. Fatt agrees with Brock *et al.* (36) that a partly blocked antidromic spike appears to sum with the synaptic potential (although a full antidromic spike abolishes it), but suggests that this apparent summation might involve the appearance of a local response. The distribution of extracellular synaptic potentials was diffuser than that for antidromic excitation, suggesting that dendrites are also involved in synaptic action. It was also concluded that the dendrites had a longer time constant (c.4msec.) than the soma (2msec.) and that the length of the synaptic potential might be due to this rather than to prolongation of transmitter action as proposed by Coombs, Curtis & Eccles (68).

Fuortes, Frank & Becker (124) have also studied the origin of motoneurone spikes with intracellular electrodes (but not by mapping the external field). They find that an inflection in the rising phase of the spike is present when the motoneurone is excited by a short pulse as well as antidromically. The partially blocked spike can still make the axone discharge (as tested by axone refractoriness). They still take the view that the more readily excitable area of the neurone (A area) is in the region of the axone hillock, although it might be "small spots scattered over soma and dendrites." Crain's (71) work on cultured spinal ganglion cells may be relevant; these have no dendrites but a single repeatedly branching "neurite." The cells have resting potentials up to 65 mV, spikes up to 95 mV, and are not spontaneously active. Excited by electrodes thrust into the culture, the response (according to stimulus strength or frequency) may be a modest "local response," or a larger "prepotential" from which a spike may arise, having a humped falling phase, and lasting up to 4 msec., followed by a positivity.

Dendrites.—The difference in time constants reported by Fatt recalls Burns' (52) suggestion, backed by a working model, that repetitive discharges of nerve cells might originate in cells in which, after activation, one part (soma) repolarized more quickly than the rest (dendrites), allowing repeated self-activation. Clare & Bishop (60) and Landau (197) showed that cortical dendrites conducted only centrifugally; had no refractory period; exhibited a cycle of enhanced excitability during the surface negative response, reduced excitability during the positivity, and increased excitability again thereafter; and could sum up depolarizations. After strychnine applied in high concentration to the cortex (62, 197), dendrite activity is depressed, and surface-positive reponses alone may be recorded to thalamic or cortical stimulation. Grundfest & Purpura (149) find that d-tubocurarine injected intravenously will abolish dendritic potentials both to synaptic excitation and to cortical excitation; and conclude that dendrites are excitable only by synapses and not directly by electrical currents. Although some of these conclusions seem incompatible, the concept of the dendrites as structures akin to motor endplates, imparting the product of a graded summation of chemical or electrical stimuli or both to the soma, from which renewed excitation may return, is of great interest.

PHARMACOLOGICAL EVIDENCE FOR CHEMICAL TRANSMISSION: CHOLINERGIC TRANSMISSION

Renshaw cell activation.—Eccles and his colleagues (82) have shown that these cells fire repetitively for several seconds after intraarterial acetylcholine (10 to 100 μg) or nicotine (0.2–2μg); eserine potentiates the former, not the latter. Dihydro-β-erythroidine 0.4 mg./kg. exerts a 10-fold antagonism to both stimulants, and reduces the Renshaw cell response to an antidromic volley. Suxamethonium, decamethonium, methacholine, arecoline, neostigmine, octamethylpyrophosphoramide (OMPA), gallamine, tubocurarine, hexamethonium and lobeline were inactive. Strychnine did not affect Renshaw cell discharge, but pentobarbitone could reduce it. This study of unit activity was supplemented by reflex studies (74) revealing impressively similar drug effects. Contrary to some earlier work (106, 174), both flexor and extensor, and both monosynaptic and polysynaptic reflexes were depressed by acetylcholine: with intact dorsal roots augmented reflex discharges were sometimes observed, abolished by dorsal root section. They suggest that failure to section dorsal roots may allow a cholinergic activation of peripheral structures (nerve endings or muscle spindles). They failed to discover in the dorsal horn or intermediate nucleus any cells other than Renshaw cells which could be activated by acetylcholine, and conclude that these cells alone mediate the effects described.

Caudate nucleus.—Intracarotid injections of diisopropylfluorophosphate produce compulsive circling in rabbits, which is associated with an asymmetrical inhibition of cholinesterase in caudate nucleus and frontal cortex (but not of other brain areas) (9). Direct injection of diisopropylfluorophosphate into the caudate, or local stimulation elicit contraversive turning in rabbits, as do methacholine, and metrazol (324). To produce localized specific effects the cholinesterase of the caudate must be reduced to 21 to 40 per cent normal; atropine abolishes the effect (323). Ablation of the caudate is known to cause ipsiversion. Forman & Ward (115) find that stereotyped contralateral movements produced by caudate excitation are unchanged by removal of the cortex. The evidence suggests that choliniceptive neurones in the caudate inhibit the upper brain-stem facilitating reticular formation.

Reticular formation.—Much of the recent work was reviewed by Dell & Bonvallet (75), Bovet & Longo (29), and Brücke (46) at the Brussels Congress. Grutta & Desmedt (76), showed, on encephale isolé, cerveau isolé, or prebulbar sectioned preparations (cat) that a number of anticholinesterases injected into the cerebral circulation could produce the cortical desynchronization, ocular signs, and reduction of auditory-evoked cortical response, characteristic of arousal. The drugs used had an activity proportional to their potency against pseudo cholinesterase, although their neuromuscular action varied according to activity on true cholinesterase. Possibly glial cells, known to be rich in pseudo cholinesterase are involved. This work seems to suggest either that pseudo cholinesterase in cells not directly involved in a synapse plays a prominent synaptic role in the central nervous system or that the inhibitors are interfering with the hydrolysis of some other ester. Longo & Silvestrini (213) found that acetylcholine by carotid injection in unanaesthetized rabbits produced arousal; eserine had little action; acetylcholine was ineffective on *cerveau isolé*. It does not seem quite clear how far direct cortical action by acetylcholine or by cholinesterase-inhibitors may cause these effects although Desmedt & Schlag (77) observed increased activity in some tegmental neurones after eserine, after section rostral to the mammillary bodies. In addition, nonspecific effects must be considered. Eccles' caution (74) about afferent stimulation was mentioned above. Nakao, Ballim and Gellhorn (236) found that the increase in cortical fast waves produced by acetylcholine was abolished by section of sino-aortic nerves (suggesting that during acetylcholine action, impulses from the baroceptors inhibitory to the hypothalamus were withdrawn). Schlag's observation (277) that the depression by acetylcholine of the pyramidal discharge to cortical stimulation (especially the I waves) could be imitated by histamine, nicotinic acid and amyl nitrite, also emphasizes the possible role of vasodilatation.

Turning to acetylcholine antagonists, Longo (212) found that atropine and hyoscine could produce cortical slow waves, and block electrical arousal to hypothalamic or fast thalamic stimulation, although the neurovegetative responses to hypothalamic stimulation, the cortical response to light, the recruiting response from the thalamus, and seizure activity to hippocampal stimulation, were unchanged. Atropine can also remove the slow cortical waves seen after electroconvulsion therapy (311), and abolishes the tremor-inducing action of Tremorine (97).

The correlation of electroencephalograph studies and behavior, however, has showed that "electrical" and actual arousal may not correspond. Bradley & Hance (33) find that amphetamine and lysergic acid diethylamide (LSD), given to animals with implanted electrodes, will indeed produce both fast waves and alert restless behavior; and that chlorpromazine can produce slow waves and "sedation," and antagonize the former drugs. But eserine, on the other hand, will produce fast waves without behavioral alertness; and if eserine is given with chlorpromazine, fast waves may coexist with a well-developed chlorpromazine sedation. Likewise atropine produces slow waves, but no sedation, and can abolish electrical arousal, although behavioral arousal takes place. When members of the two groups of drugs, i.e. LSD, amphetamine, or chlorpromazine on the one hand, eserine, or atropine on the other, are combined, it seems that the former determine the physiological state, the latter the electrical record.

Medulla.—Diisopropylfluorophosphate injections into the medulla cause turning movements (324): and tetraethyl pyrophosphate (TEPP) injected into the fourth ventricle causes a considerable increase in the hyperpnoea to stimulation of Hering's nerve (225).

Adrenergic Transmission

Spinal cord.—Previously Schweitzer & Wright (281) had found epinephrine to depress the knee jerk. Burn, Bülbring & Skoglund (51) observed variable effects, and obtained evidence that the presence or absence of adrenaline modified cord responses. Bernhard & Skoglund (20) showed that both epinephrine and norepinephrine increased the monosynaptic reflex (and the P wave of the cord potential), but reduced flexor mono- and multisynaptic reflexes. Wilson (328) finds that epinephrine increases the monosynaptic reflex in low doses, but with high doses depresses it. Eccles and his colleagues (74), however, could record no effects with epinephrine save late ones, possibly due to vascular changes. Angelucci (8) failed, even with epinephrine 10^{-4}, to affect reflexes of frog spinal cord.

Reticular system.—Dell & Bonvallet (75) and Bovet & Longo (29) review much of the work implicating adrenoceptive structures in reticular arousal. Slocombe, Hoagland & Toazian (290) find that the anaesthetic used is critical; in the animal under thiopentone, epinephrine reduces frequency and amplitude of cortical activity, but not in the etherized animal. Nakao *et al.* (236) find that, in cats under light thiopentone anaesthesia, epinephrine and norepinephrine increase the slow potentials in the cortex, producing a picture like full barbiturate anaesthesia; this change is abolished by sino-aortic denervation, and they think that excitant action on the reticulum is seen only with big doses. Rothballer (270) records both cortical "activation" and "deactivation" by epinephrine in unanaesthetized cats; after thermocoagulation of the pontomesencephalic reticulum epinephrine was effective, but carrying the lesion up to mesodiencephalic border abolished epinephrine effects. Longo & Silvestrini (213) found that epinephrine in rabbit had little activating action, and might sedate. Milŏsević (226) finds that epinephrine intensifies both the anaesthesia produced by thialbarbitone and other anaesthetics, and also the convulsant action of strychnine, nicotine, and cocaine. Among nonspecific effects, it is worth noting Schmitt's (278) observation that although with high blood pressures small doses of epinephrine and norepinephrine reduce brain volume, after lowering the blood pressure the same doses produce a large rise in cerebral volume; the volume changes are often more prolonged than the blood-pressure effects. Abrahams & Pickford (1) find that epinephrine in low dosage can prevent the antidiuretic effect of acetylcholine, but high doses do not do this. They discuss the possibility of a neurone inhibiting the choliniceptive supraoptic neurones, stimulated by low doses and paralyzed by high doses of epinephrine.

It seems to the reviewer, taking also into account Marrazzi & Hart's (220) demonstration that epinephrine paralyzes transcallosal transmission and the action of epinephrine on ganglia (223) that excitation (as opposed to facilitation) of nerve-cells by epinephrine is still to be demonstrated. It may be noted that although amphetamine is often regarded as sympathomimetic, this is probably incorrect, and experiments with it cannot necessarily be used as evidence of adrenoceptive processes; amphetamine appears to have closer connections to 5-hydroxytryptamine (314). A modulating action by epinephrine is more readily accepted as a possibility. Loewenstein (211), on the basis of the effect of sympathetic stimulation and of epinephrine on sensory discharges from frog skin, goes so far as to coin the term "modulapse" for the situation where the function of one neurone is modulated by another, in the absence of normal transmission. But since applied currents (anode outside) have the same action, and epinephrine can reduce the standing potential (outside negative) across frog skin, the action of epinephrine here may arise from reduction of the skin polarization rather than from any specific neuronal action.

Tryptaminergic transmission

Gaddum (125) has reviewed the distribution and action of 5-hydroxytryptamine (HT). Gaddum & Vogt (127) have confirmed Feldberg and Sherwood's observation that 5-hydroxytryptamine intraventricularly produces a lethargic state, although they found it persisted several hours. The other actions of 5-hydroxytryptamine described earlier (potentiation of barbiturate anaesthesia, antagonism to strychnine, reduction of flexor reflexes, reduction of transcallosal transmission) are also largely depressant, although on autonomic ganglia a stimulant action can be demonstrated (306, 307), and 5-hydroxytryptamine can excite sensory endings (10). Release of an 5-hydroxytryptamine-like substance from the frog spinal cord, increased by reflex excitation, was reported by Angelucci (8). Paasonen & Vogt (243) find that brain 5-hydroxytryptamine is not changed by administration of ephedrine, ether, insulin, or β-tetranaphthylamine, but amphetamine reduces it about 50 per cent. Fastier *et al.* suggest (100) that hypnosis-prolongation by 5-hydroxytryptamine may be secondary to its hypothermic effects. Bonnycastle *et al.* (27) find that a number of anticonvulsants raise 5-hydroxytryptamine in brain (but not in gut or spleen); but raising 5-hydroxytryptamine by giving iproniazid or 5-hydroxytryptophan did not protect against leptazol convulsions.

The action of 5-hydroxytryptamine has been inculpated in the effects produced by other drugs, especially reserpine (for a general review see ref. 16) and lysergic acid diethylamide (LSD), which deserve separate discussion.

Reserpine.—The interpretation of reserpine action only in terms of 5-hydroxytryptamine mobilization must be modified since Muscholl & Vogt's (234) discovery that sympathin as well as 5-hydroxytryptamine is released in the brain. Falls in plasma 5-hydroxytryptamine (146) and plasma sympathins (181) after reserpine are also reported. In an animal treated with iproniazid, reserpine does not reduce brain 5-hydroxytryptamine, and its action becomes more like that of lysergic acid diethylamide (58, 286). Reserpine is known to elicit the alerting reaction (265), to facilitate convulsants such as camphor, caffeine, nikethamide, leptazol, and strychnine or electric shock (22, 57) (although anticonvulsant action can be detected, 57), to antagonize anticonvulsants (57), to antagonize morphine analgesia, to produce emesis in pigeons, and to increase the monosynaptic reflex (280). On the other hand, it can depress the "search and flight" reaction of the rabbit to hypothalamic stimulation (238), reduce sham rage in the cat (280), depress the reflexes of frog spinal cord (8), modify conditioned avoidance behavior in monkeys (292), prolong barbiturate anaesthesia (an action prevented by the bromo derivative of lysergic acid diethylamide (BOL) and lysergic acid diethylamide) (274) and, if given subcutaneously, synergize with 5-hydroxytryptamine given intraventricularly (127). Reserpine has a modest spasmolytic action reversed by components of the tricarboxylic acid cycle (136) but a negligible anti-cholinesterase action (284).

Gangloff & Monnier (129) find 5-hydroxytryptamine more like reserpine than chlorpromazine in its central effects. But (23) 5-hydroxytryptamine lacks both the ability of reserpine to synergize with convulsants, and also the ability to modify this action of reserpine: this argues against reserpine action being due either to a temporary flooding of the central nervous system with 5-hydroxytryptamine, or to a subsequent deprivation of the area of 5-hydroxytryptamine resulting in increased excitability. Brodie *et al.* (38) made the interesting suggestion that the inability of the brain to bind 5-hydroxytryptamine after reserpine, combined with continued 5-hydroxytryptamine synthesis, leads to a persistent low level of 5-hydroxytryptamine and that this, rather than reduction of stored 5-hydroxytryptamine produces reserpine's effects. It is not clear, however, why, after an initial flooding, the level of free 5-hydroxytryptamine should be any higher than in the normal animal unless the rate of 5-hydroxytryptamine formation varies inversely with level of bound 5-hydroxytryptamine. No evidence for such a control of 5-hydroxytryptamine synthesis yet exists.

Reserpine action may become interpretable in terms of a conjoint 5-hydroxytryptamine and sympathin release, leading to an initial flooding of the central autonomic regions with these hormones, followed by a local lack, and a peripheral sympathetic inactivity from lack of sympathin in post-ganglionic neurones. But the cortex may also be involved, since reserpine's depressant action on conditioned avoidance by monkeys is reduced by cortical ablation, especially of the temporal lobe (292); and Schneider *et al.* (280) concluded from observations on thalamic cats that the cortex was necessary for some of reserpine's actions, perhaps because the drug intensified cortical inhibition of the diencephalon.

Lysergic acid diethylamide (*LSD*).—The discovery that lysergic acid diethylamide was a powerful anatagonist to 5-hydroxytryptamine on blood vessels, bronchi, rat uterus, and guinea pig ileum (D receptors only), prompted the notion that its hallucigenicity was caused by such an antagonism centrally (125). This view now seems less likely for the following reasons: (*a*) hallucinations are produced by other indolic compounds of feeble anti-5-hydroxytryptamine action (harmine, hashish, adrenochrome, bufotenin) and by some quite unrelated substances (e.g. nalorphine) (167): (b) other effective anti-5-hydroxytryptamine substances (such as the bromoderivative, BOL) fail to reproduce the characteristic LSD actions (127, 273); c) although lysergic acid diethylamide can temporarily reverse the lethargy induced by intraventricular 5-hydroxytryptamine, other drugs such as morphine and methadone can do it equally well, and 5-hydroxytryptamine cannot reduce lysergic acid diethylamide action (127).

It might be suggested, on the other hand, that the action of lysergic acid diethylamide on the brain is 5-hydroxytryptamine-like, since in appropriate dose it can stimulate smooth muscle (125) and its hallucinogenic action is abolished by BOL (137); Marrazzi & Hart (220) found that lysergic acid diethylamide and 5-hydroxytryptamine both depressed transcallosal transmission, and Slocombe *et al.* (290) found that lysergic acid diethylmide and 5-hydroxytryptamine, had similar actions on cortical activity in the rat under pentothal. But the stimulant actions of lysergic acid diethylamide, causing electrical and behavioral arousal (33), brief sham rage when given intraventricularly (127), characteristic disturbances in waltzing mice, spiders and fighting fish, and a pyrogenic-type reaction of diencephalic origin (125, 240), cannot be matched by 5-hydroxytryptamine. On this view, too, it is hard to explain the actions shared by LSD and BOL, in antagonizing the potentiation of hexobarbitone, anaesthesia by 5-hydroxytryptamine or reserpine (274).

Tolerance occurs both to the hallucinogenic (167) and pyrogenic actions of lysergic acid diethylamide (240). Rothlin (271) reviews its pharmacodynamics. On the reticular arousal, Bradley (31) suggests that chlorpromazine and lysergic acid diethylamide act in relation to the afferent inflow to the reticular system, whereas amphetamine changes the threshold for direct reticular excitation. Winter & Flataker record (329) a partial anatagonism by 5-hydroxytryptamine, and a potentiation by reserpine, of the interference by lysergic acid diethylamide with rat rope-climbing. A very interesting development is the observation that lysergic acid diethylamide can (in high doses) reduce the post-synaptic geniculate response (95), inhibit recruiting from the centrum medianum of the thalamus while specific responses are enhanced (261), and facilitate visual and auditory cortical evoked responses in low doses (260). The primary facilitation of the auditory response is antagonized by reserpine (260).

Amphetamine.—This substance has often been regarded as primarily a sympathomimetic drug: but it appears that its action on isolated smooth muscle preparations and on the blood pressure is largely "tryptaminomimetic" (314). There is even evidence for some nicotinic action (184). It is noteworthy that Longo (212) found it aroused effectively when epinephrine did not. Amphetamine resembled lysergic acid diethylamide in producing both electrical and behavioral arousal, and could be antagonized in both respects by chlorpromazine (33); and it lowered the threshold to reticular stimulation (31). Paasonen & Vogt (243) showed that amphetamine would reduce brain 5-hydroxytryptamine about 50 per cent. Gaddum & Vogt (127) found that amphetamine intraventricularly produced vomiting and then a lethargy which intensified 5-hydroxytryptamine action by the same route; parenterally, however, it exerted its usual analeptic effect, and antagonized 5-hydroxytryptamine.

Mescaline.—When injected into the ventricles mescaline produces a "catatonic" state in cats and dogs after initial autonomic stimulation (299); the action is fully inhibited by chlorpromazine; reserpine lessens the catatonia; azacyclonal changes the responses so that excitation is more prominent. In high concentration topically it has a strychnine-like action on the cortex and lateral geniculate body (272). Vane (314) finds it to be primarily 5-hydroxytryptamine-like rather than sympathomimetic. The extensive but shaky theory of M-substance in schizophrenia, and its relation to hallucinogens such as mescaline, adrenochrome, adrenolutin, and other compounds, has been reviewed (171).

Substance P

Angelucci (8) records a release of a substance that might be Substance P from frog spinal cord. Brain Substance P is unaltered by amphetamine, ephedrine, insulin, β-tetranephthylamine, caffeine, ether, or reserpine (243). Substance P given intravenously in cat does not modify ganglionic transmission or the vascular response to carotid occlusion; intraventricularly a stimulation of respiratory frequency and depth occurs, and a loss of "spontaneity" in the animal's behavior (94). Applied to a perfused rabbit ear isolated save for nervous connections, it provokes a reflex stimulation of respiration and fall of blood pressure; hexamethonium does not prevent this (although it antagonizes the similar response to acetylcholine), but cocaine abolishes the response to P (201). Minz & Walaszek (227) find an increase of Substance P in rabbit brain after treatment with serum from schizophrenics.

Inhibitor Substance of Florey (I)

Brockman & Burson (37) find that glutamic acid and aspartic acid as well as γ-aminobutyric acid can inhibit the opener system of crayfish claw, implying that γ-amino butyric acid (or its derivatives) may not be wholly responsible for I activity in an extract. I appears in fluid bathing the cortex (112). In the first experiments (112) on its effects, it was only active in acid solutions. Paralysis of inferior mesenteric and stellate ganglia, but not of superior cervical ganglion or of neuromuscular transmission, was produced. Applied to exposed spinal cord (113) it depressed the stretch reflex, but potentiated or even elicited the flexor reflex. An odd feature was the speed with which effects were produced (a few seconds); this is too soon for any reasonable rate of diffusion to the gray matter, and prompts the doubt that the effects were due to a nonspecific effect on surface structures, perhaps temporarily exciting nociceptive afferent fibres. Florey (111) finds a marked accommodation, both to I, the inhibitory substance, and to acetylcholine, by the crayfish stretch-receptor, such that when acetylcholine is washed out a period of silence in the discharge ceases, and when Florey's inhibitory substance I is washed out, the receptor is activated.

An interesting link with this work lies in the convulsant action of semicarbazide and related compounds (186, 187). The convulsions develop only after a latent period of about one hour, and are associated with a reduction of γ-aminobutyric acid in the brain, probably due to inhibition by the semicarbazides of the pyridoxine-dependent enzyme glutamic acid decarboxylase. Pfeiffer and his colleagues (256) find that the convulsions are prevented by pyridoxine and certain anticonvulsants, and that in cats convulsive activity begins first in the aqueductal gray matter and head of the caudate. Semicarbazides also antagonize histaminase (11) and can produce beak and bone deformities in chick embryos (241).

General Physiology

Spinal cord.—Frank & Fuortes (118) record data on the electrical constants of motoneurones. Membrane deplorization required for excitation is about 1 mV less by synaptic than by direct excitation: accommodation is less prominent than in nerve. Fuortes & Hubel (123) have brought out the role of temporal summation in extensor, as opposed to flexor, reflexes, and Granit *et al.* (141) have used post-tetanic potentiation to distinguish tonic and phasic motoneurone discharges to a stretch of ankle extensors. Lloyd and Lloyd, & Wilson (208, 209, 210), have analyzed in detail the monosynaptic response with repetitive excitation at various rates.

Brooks *et al.* (40) find that bulbar or suprabulbar stimulation may inhibit spinal reflexes without impairing antidromic respones, posttetanic potentiation, or the facilitation of antidromic responses by orthodromic excitation; they conclude that the inhibitory process is postsynaptic. Lindblom & Ottosson (205) find fibres in the pyramidal tract depressing the N_1 dorsum potential (to low threshold skin afferent stimulation). Eccles, Fatt & Landgren (83) have verified that the inhibitory neurones activated by Ia or Ib fibres have the low threshold, specificity, frequency of discharge and lack of subliminal fringe required if they are to act simply as "phase-switches" from excitation to inhibition in muscle reflex paths. Edisen (87) proposes that, if synaptic excitation in a motoneurone occurs in dendrites and saltates from dendrite to axone, inhibition could be produced if the concomitant soma depolarization increased membrane conductance more than the electrotonus transmitted through soma membrane assisted axonal stimulation.

Frank & Fuortes have followed an earlier paper (116) describing the neural structures encountered when a microelectrode is passed through the cord, by an account of the properties of interneurones (117). Diverse response patterns occur, and antidromic shocks activate some cells (Renshaw cells) but silence others, implying that Renshaw cells play on interneurones as well as motoneurones. Skoglund & Kolmodin (289) have analyzed the convergence on interneurones in the lumbar region. Gelfan & Tarlov (131) describe a drastic but apparently partially reversible method of modifying spinal cord responses, by compressing about 5 mm. length of cord with suprasystolic pressures. McCouch & Austin (215) have further analyzed the N_1 and N_2 waves of the cord potential. Ethyl alcohol depresses mono- and multi-synaptic reflexes equally (192).

In an elegant series of papers, Laporte, Lundberg *et al.* (173, 198, 199, 200, 214) have studied the properties of the dorsal spino-cerebellar tract, using the dissected fascicle. Muscle nerve stimulation yields synchronous volleys, and intra-axonal records show that single shocks produced single spikes; with skin nerves, repetitive discharges occurred with fibres firing up to 16 times per stimulus at frequencies up to 1000/sec. Cerebellar projection was mapped out. Muscle-spindle and Golgi-tendon organ responses were identified, sometimes converging on to the same neurone. Activity in the tract depends partly on interneuronal activity. The transmission process in Clarke's column appears to be very efficient, comparable to that in the cuneate nucleus (302), the intermediate nucleus (83), and perhaps the lateral geniculate (25). Post-tetanic potentiation is present, though small. Yamamoto *et al.* (334) have studied the afferent inflow to the posterior columns.

Despite the vogue for chemical transmission, interest is maintained in the role of slow or steady potentials. Gopfert (139) has restudied the dorsal root potential of frog spinal cord; it is remarkably resistant to asphyxia or storage of the cord in the cold. If the cord substance is almost entirely removed from the root so that only a few neurones can be found histologically, a dorsal root potential of 1 mV can still be recorded with external electrodes. Koketsu (191), using impaled dorsal root fibres in the funiculus of bullfrog isolated cord finds, with a shock subthreshold for the impaled axone, that a slow inside-positive potential is recorded, about 4 mV in magnitude, which is not recorded outside the fibre; he concludes that the central ending of dorsal root fibres is depolarized secondarily by the activity of other dorsal root fibres or interneurones. Wall *et al.* (319) have analyzed excitability changes in terminal arborizations of spinal afferents; for skin afferents, hyperexcitability may persist over 150 msec.

Cortex.—A valuable critical discussion of cortical structure and function will be found in Sholl's book (285). Beurle (21) has analyzed mathematically the properties of a mass of cells with neuronal properties; such a system would allow the propagation of waves of activity under definite conditions, and furnishes a model for conditioning, learning, and memory.

Spreading depression has received considerable attention. Grafstein (140) has shown that a burst of intense activity, followed by cortical depression, signals the advance of the negative wave: evidence is advanced in support of the suggestion that the depression is transmitted by K^+ release. It is known that spreading depression propagates at 2 to 5 mm/min. as a 10 to 15 mV surface negative wave, followed by surface positivity; it resists brief asphyxia, is abolished by topical cocaine, crosses a cortical cut if the edges are coapted (but not a scar, 157) and resists barbiturates but is reduced by ether. There is a rise of cortical impedance (154) and an increase in local blood flow (296). Species variations exist (156) such that the reaction can only be elicited once in monkey, occasionally in cat, and every 6 to 10 min. in rabbit in whose cortex it spreads widely. As an animal grows, the development of the injury potential recordable from the cortex goes parallel to the capacity for showing spreading depression (48). Metrazol or photic stimulation after metrazol may produce it in the rabbit (155) in which spreading depression may be a protective mechanism.

Burns, Grafstein & Olszewski (53) have shown that the cells responsible for the "burst" response and after-discharge are mostly in layer V, are among the largest neuroses, include but do not only consist of Betz cells, and have connections lying in layers IV and V. Hunter & Ingvar (177) have analyzed the paths (cortical, subcortical, and possibly a third more complex path) by which irradiation from visual to other cortical areas occurs of the response to a light-flash after metrazol. Bernhard and colleagues (18, 19) find lidocaine very effective in controlling cortical seizures, acting at cortical level, without affecting nonconvulsive activity.

Projections from the cortex have been studied (326) including those which affect the N_1 cord dorsum potential (205), or involve the intralaminar thalamic nuclei (239), the dorsomedial thalamus and pons (293), and the brainstem reticulum, pons and medulla (268), or control tegmental conduction (2). The pathway of the sympathetic vasodilator system (distinct from the hypothalamic autonomic system) has been mapped out from the motor regions of the cortex downwards (206). Spatial organization of the corticospinal tract has been found largely to disappear below the internal capsule; the dorsal spinocerebellar tract splits the tract in the cervical region (15).

Projections to the cortex analyzed include thalamic projections from the ventrolateral nucleus to motor cortex (202) which yield responses possibly from cells superficial to pyramidal cells and accompanied by arrest of cortical activity; from posterior ventral nucleus to sensory cortex mediated by a monosynaptic path firing at rates up to 500/sec.; and from medial thalamic regions (203), mediated by a long-latency recruiting path to several cortical layers. Lesions of ipsilateral ventral posterior thalamic nuclei produce a supersensitivity of sensory cortex to methacholine and metrazol (297). Clare & Bishop (61) contrast the two types of responses to stimulation of lateral dorsal and medial dorsal nuclei: a short latency response unchanged or fading on repetition at 6/sec., and a longer latency response of higher threshold, longer duration, which "recruits." The latter response shows a supernormal phase at 1/6 to 1/8th sec. which the short latency response lacks. They suggest that the fast response may be of small myelinated fibres, the slow response that of nonmyelinated fibres, and that the "recruitment" may be a misnomer for a local increasing activity in particular dendrites. Jasper, Naquet & King (179), stimulating the intralaminar n. centralis lateralis, obtained vigorous recruiting responses over wide cortical areas, including sensory cortex, but point out that failure to find it in sensory cortex may be due to a poor preparation, incorrectly placed stimulating electrodes, or excessive sensory activity. Brookhart & Zanchetti (39) distinguish carefully the "augmenting" and the "recruiting" response (the latter being generalized, slowly developing, with long latency and minimal initial positivity). The "augmenting" response appears to correspond most closely to spontaneous spindle bursts, as judged by their influence on pyramidal discharges.

Kruger (195) has studied the evoked responses in precentral gyrus to somatic afferent volleys (fast cutaneous or slow muscle afferents); these responses do not arise from postcentral or anterior cortex, and survive pyramidal section or cerebellar ablation. The cortical responses to nociceptive stimuli are radically modified by varying depth of anaesthesia (237). The cortical and other responses evoked by light have been analyzed by Bremer & Stoupel (34), Malis & Kruger (217) and Harman & Berry (153) and unitary auditory responses by Erulkar *et al.* (91). Baird & Spiegel (13), Cragg & Hamlyn (70) and Blackstad (26) report work on hippocampal and amygdaloid regions.

Subcortical and mesencephalic structures.—Feldberg (105) has discussed the types of response resulting from intraventricular injections: (*a*) convulsions corresponding to centrencephalic epileptic seizures, produced by small doses of d-tubocurarine (108); (*b*) a condition resembling surgical anaesthesia, elicited by epinephrine, norepinephine and ergotamine; (*c*) a catatonic state induced by bulbocapnine (109) or anticholinesterases. Although this work has not allowed any definite statement about transmission at any histologically specified synapse, these general reaction patterns are of interest, particularly in conjunction with the distribution of hormones and of diffusely reacting neuronal systems in the periventricular regions. The method has been widely used; it has even been applied with similar results to the mouse (150, 151). The observation that injections of glucose into the cerebral spinal fluid cannot prevent the effects of systemic insulin hypoglycaemia on the spinal cord indicates that drugs so injected can have only a limited penetration (330). Similar centrencephalic seizures to those produced by d-tubocurarine are elicited by injections of procaine-penicillin into the lateral nucleus of thalamus, putamen, globus pallidus or brain stem (98), and penicillin injections into non-specific thalamic areas evoke synchronized $3\frac{1}{2}$ to 5/sec. cortical spindles (298). Penicillin and strychnine have also been used in analyzing thalamo-caudate-pallidal connections (263). Bulbocapnine has been tried for sedation of children for electroencephalogram recording (12). Fukuma (122) reports on the central effects of veratramine. Gangloff & Monnier (128), from a comparison of the effect of various anticonvulsants on excitability of diencephalon, rhinencephalon, and cortex concludes that diencephalic action by such drugs confers protection to *grand mal*, and diencephalic and cortical action is required to protect against *petit mal*.

Parma & Zanchetti (245) find that judicious reticular stimulation can selectively depress the surface negative phase of the augmenting response to slow thalamic excitation; the fact that pyramidal discharge still accompanies the positive phase confirms the association of these two. Anaesthetics rapidly produce cortical desynchronization (an effect removed by mesencephalic section) and abolish strychnine's local cortical effects (269). Chloralose activates the human electroencephalogram (231). Wycis *et al.* (333) have analyzed the tremor produced by tegmental stimulation. Scheibel *et al.* (276) describe the extensive convergence of diverse afferent pathways on the reticular system. Papez gives an account of the central reticular pathways (244). It is claimed that reticular excitation can influence the state of consciousness in monkeys (258). An interesting study by King (188) shows that barbiturates strongly depress arousal, depress reticular response to sensory stimulation, favor recruitment, and leave cortical responses to sensory stimulation unchanged. Mephenesin, on the other hand, does not influence arousal, but depresses recruitment, sensory cortical responses and reticular responses to sensory stimulation. Mephenesin can remove the enhanced recruitment induced by barbiturates but not the depression of arousal; but barbiturates can restore recruitment depressed by mephenesin. This seems to imply that mephenesin does not attack recruitment directly, but depresses some facilitating mechanism, the loss of which can be offset by the withdrawal (under barbiturates) of desynchronizing reticular influences. Sharpless & Jasper (282) have analyzed habituation of the arousal reaction, distinguished two types of arousal, and discussed the pathways involved.

Responses to intravenous beta-hypophamine (Pitressin) (but not to ephedrine or epinephrine) in the region of the mammillary bodies are described (300). Injections of hypertonic solutions led to electroencephalogram changes, and if repeated, to seizures in amygdala or hippocampus, implying that osmoreception may be more extensively distributed than the preoptic region. Purpura (259), by cross-circulation experiments, has found stimulation of bulbar reticulum of one animal to lead to humoral activation of the recipient's cortex. It is hard to believe that a reticular transmitter should be detectable after crossing two blood-brain barriers and mixture with a large amount of blood, but a generalized release of reticular hormones might be responsible.

Bishop & Evans (25), studying the optic tract synapse in the lateral geniculate body, find the postsynaptic response supernormal while the tract is still partially refractory; postsynaptic response varies linearly with tract activity, and brief discharge rates up to 1000/sec. are seen. With continued excitation, steady potentials (soma region as sink) can be recorded (315). Post-tetanic potentiation can be shown as well as post-tetanic subnormality (95, 176); prolonged tetani can remove the subnormality resulting from briefer tetani (96). The effects of mescaline and lysergic acid diethylamide have been tested (272). Unitary responses in the medial geniculate body and the effect of morphine have been analyzed (316).

Cerebellum.—Granit & Phillips (143, 144) have made a fascinating study of unit responses by Purkinje cells, deserving extensive discussion. Prepotentials (often at rates of 200/sec.) were recognized, attributed to the massive dendritic input to a Substance P-cell, but no "generator potential." Two kinds of inhibition were found, one apparently a cathodal depression (attributed to basket cell activation) and usually occurring spontaneously, the other probably hyperpolarizing, and elicitable by stimulation. Grant, Holmgren & Merton (142) have shown that cooling or removing the anterior lobe of the cerebellum in the cat "switches" the response to ear-twisting from γ to α pathways; they suggest that this part of the cerebellum determines the body's choice between movements controlling muscle-length (plastic in character and dorsal-root-dependent) and movements controlling muscle-tension (nonplastic and independent of afferents). The characteristic loss of length (position) control in patients with cerebellar lesions conforms well with the suggestion. Evidence as to the role of γ-fibres comes also from the experiments by Matthews & Rushworth (221, 222) on the effect of procaine (which paralyzes γ-fibre activity first) on stretch reflexes. γ-fibres are also particularly sensitive to x-irradiation (132). Projections to the cerebellum from splanchnic afferents (327) and dorsal spinocerebellar tract (228, 229) and from the deep nuclei (55) have been examined, as well as the mechanism of the crossed disappearance of extensor rigidity following caudofastigial lesions (230). X-irradiation (4) and DDT (2-2 bis (parachlorophenyl) (1-1-1 trichloroethane)) (242) produce interesting specific cerebellar lesions.

Area postrema.—Brizzee (35) finds that thermal coagulation of the region in monkey abolishes the emesis after x-irradiation, although a similar lesion to the nearby dorsal vagal nucleus had no effect. Clemente & van Breeman (64) have shown the area to be full of fine unmyelinated fibres, and some thicker ones, entering from its lateral aspect, terminating on the cells there or on blood vessels. Clemente, Sutin & Silverstone (65) have also shown that intravenous injections of hypertonic saline lead to increased nervous activity in this area.

Effects of Certain Drugs

Strychnine.—Eccles and his colleagues (69, 74, 82) have established that strychnine depresses or abolishes inhibitory postsynaptic potentials but not excitatory postsynaptic potentials. Its interference with Renshaw cell effects is exclusively at the Renshaw axon endings. The question arises as to why strychnine is so ineffective on some types of inhibition, such as the inhibition of Head's diaphragmatic slip by lung inflation (Creed & Hertz, 72). Bradley, Easton & Eccles justly point out (32) that in a polysynaptic inhibitory reflex, removal of inhibition at intermediate relays might intensify the final discharge; but it is hard to imagine that it would be so intensified as to restore to normal the final postsynaptic response, in the presence of enough strychnine to paralyze another inhibitory synapse completely. An obvious possibility is that there is a second, strychnine-resistant, inhibitor.

Cobb *et al.* have analyzed (66, 67) the spike response to photic stimulation after strychnine, and find spike activity to be transmitted along neuronal chains in the deeper cortical layers. Terzuolo & Gernandt (301) have correlated unit discharges with spinal cord potentials during strychnine tetanus. Clare & Bishop (62) used strychnine to poison cortical dendrites.

d-Tubocurarine.—This drug continues to be used by intravenous route without adequate control. Its ability to release histamine, for which it is a standard drug (see (249) for references), is a serious complication only to be controlled by use of an equiactive histamine-liberator, or by previous exhaustion of releasable histamine; records of blood pressure or comparisons with injected histamine or epinephrine, do not allow an adequate estimate of the effects of the release. The ability of heparin to antagonize apparent central actions of d-tubocurarine (262) almost certainly rests on complex-formation between the two drugs (249). The ability of d-tubocurarine to paralyze ganglia and the γ-endplates must also be considered.

Tetanus and Botulinum toxin.—Brooks, Curtis & Eccles (42) establish clearly that tetanus toxin resembles strychnine in antagonizing the production of inhibitory postsynaptic potentials while being inactive on excitatory postsynaptic potentials, or on the cholinergic Renshaw cell synapse. This does not altogether agree with the known pharmacology of tetanus toxin [confused though it is (332)], for which a cholinergic mechanism of one sort or another has usually been envisaged (6, 159). Botulinum toxin, tested on miniature end plate potentials reduces their frequency but not their size (41), and can be antagonized by post-tetanic potentiation.

Morphine.—The actions of morphine and morphine-substitutes on guinea pig ileum show a striking parallelism with their activity centrally. This lends some importance to the finding that low concentrations of morphine depress acetylcholine output by the gut, both in the resting state (253, 275a) and when its nervous tissue is excited (253). It is even possible to produce "tolerance" and "dependence" in the ileum *in vitro* (253).

Tranquillizing drugs.—The rapid multiplication of these drugs has not simplified the pharmacology of the central nervous system. The classification (17) as (*a*) phenothiazine derivatives, e.g., chlorpromazine; (*b*) reserpine-like; (*c*) diphenylmethanes; (*d*) substituted propamediols, is helpful, but other structures are important. (The following references to these and related agents, may be noted: 14, 17, 24, 31, 33, 43, 129, 165, 166, 175, 180, 219, 238, 255, 257, 264, 275, 279, 287, 299, 321).

Blood-Brain Barrier

A major obstacle to pharmacological study is the existence of the so-called blood-brain barrier. Feldberg, Malcolm & Sherwood (108) and Eccles *et al.* (74, 82) have encountered again the well-known failure of quaternary or strongly water soluble substances to penetrate the central nervous system [cf. Burgen & Chipman (50)]. The heroic experiment by Smith *et al.* (291), in which a conscious subject received three times the respiratory paralyzing dose of d-tubocurarine, but retained mental function and memory completely unimpaired, remains a classical demonstration of the failure of the drug to produce central actions. The observation (248) that cerebrospinal fluid levels of hexamethonium may be less than one per cent of the plasma level, even after a lapse of 1 to 2 hr., emphasizes the same point. Mayer & Bain (224) have attempted to localize the barrier with fluorescent quaternary compounds, and place it in the region of the outer wall of the capillary edothelium and glial plasma membrane. The barrier is present (145) in 12 day rat embryos, when neither astrocytes nor Hess' ground substance are developed. Koelle & Steiner (190) compared the reduction of brain cholinesterase achieved by parenteral and intraventricular injections of two phosphorous antiesterases, one quaternary, one tertiary; parenterally the quaternary had negligible action, although 1/100th dose was strongly effective intraventricularly. Evidence of the simultaneous presence of the quaternary compound and active acetylcholinesterase in brain tissue was obtained, and is regarded as a possible model for the occurrence of acetylcholine and cholinesterase within a single cell. CO_2 inhalation (10 per cent or more) increases the penetration of trypan blue into rabbit brain, but the effect ceases with the inhalation (63).

Autonomic Ganglia

R. M. Eccles (85) has reported her experiments with intracellular electrodes. Resting potentials of 65 to 75 mV were seen. Spikes were up to 90 mV, of 4 to 7 msec. duration with an inflection (identified as synaptic potential) on the rising phase, and followed sometimes by an afternegativity of 1 to 5 mV preceding the usual slow positivity. Synaptic potentials, giving rise to a spike at about 15 mV, lasted about 60 msec. in the absence of a spike. In later experiments (cited J. C. Eccles, 81) antidromic spikes were recorded, with the "IS–SD" transition, "SD" responses sometimes failing to appear. A subsequent paper (86), in which external electrodes were used as in earlier studies (84), describes the effect of nicotine on isolated rabbit ganglia. The ganglion depolarization and change in after-potentials described by Paton & Perry (247) are confirmed; it was found in addition, that with repetitive stimulation, nicotine led to more marked afterpositivity, and that nicotine reduces the synaptic potential obtained under dihydro-β-erythroidine (sometimes after temporarily restoring a spike) and the "late negative" wave.

Pascoe (246), on a similar preparation, describes depolarization produced by acetylcholine in the presence of an antiesterase, by tetramethylammonium salt or nicotine, which is followed by a large positivity on washing out. The depolarization is insensitive to temperature but the positivity is increased by moderate cooling (maximum at 30°C.) and almost disappears at 2 to 3°C. or 40°C. Hexamethonium reduced both effects evenly, and behaved like a competitive blocking agent, but d-tubocurarine removed the positivity selectively.

Hutter & Kostial (178) find that although perfusion of a ganglion with Ca-deficient Ringer produces block, perfusion with isotonic NaCl does not. It appears that K is needed to bring out the effect of Ca lack on the ganglion. Gertner & Reinert (133) conclude that K_i changes are not responsible for the reactions of a denervated ganglion, but that losses of amino-acids are more likely. Trendelenburg (306, 307, 308) has obtained further evidence that 5-hydroxytryptamine, like histamine and pilocarpine, produce a stimulant action resistant to hexamethonium and d-tubocurarine, but abolished by cocaine and during the first phase of nicotine's ganglionic action. He also finds (309) a central stimulant effect of histamine by ventricular injection. Malmejac (218) has studied the splanchnic-suprarenal medulla "synapse," finding that small doses of epinephrine facilitate and large doses depress transmission. Matthews (223), on the other hand, finds epinephrine and norepinephrine in small doses only depressant on the cat superior cervical ganglion, although isoprenaline augmented submaximal responses.

Recent work on ionic fluxes and peripheral nerve promise to illuminate ganglionic responses. Thus ouabain reduces Na efflux and K influx in red cells (138, 294); low K_0 has a similar action; and denervation of a muscle reduces K influx (158). It is interesting that ouabain and denervation sensitize the ganglion to acetylcholine, and low K_0 or denervation bring out a ganglion-stimulant action by hexamethonium. It may well be that specific membrane changes underly these effects rather than the metabolic alterations previously postulated.

There is also a striking analogy between the hyperpolarization and spike augmentation after repetitive stimulation of C-fibres and of ganglia; the afterpositivity studied by Pascoe may be related. The glial cloak to the ganglion cell and its processes has already been invoked to account for some of the differences between ganglionic and neuromuscular potential changes (248a), and a parallelism is obvious to the diffusion barrier postulated by Ritchie & Straub (266, 267). The dendrites of the ganglion, embedded in their glial envelope, could then be the seat of a positivity due to sodium pump activation and K_0 depletion in the spaces around the fibre. On the other hand, when the ganglion is partly blocked (so that, perhaps, predominantly soma response is seen), late negative waves are more prominent; here the situation may be more analogous to a large diameter structure such as the squid axone, in which the barrier to diffusion near its surface raises K_0 sufficiently to cause a negative afterpotential.

Collateral Sprouting

Murray & Thompson (233) have found that the return of function after partial preganglionic denervation (288) is due to the development of sprouts from the remaining intact preganglionic fibres. The response is remarkably prompt (sprouts are visible histologically in a few days) and effective (10 per cent of fibres will suffice to restore function completely). Supersensitivity appears during the early stages of the denervation, but disappears as reinnervation by sprouts becomes complete (at about 30 days). The sprout synapses are not fully normal, as acetylcholine output is a little below normal, and they are more than normally sensitive to blocking agents. A rerouting of autonomic pathways occurs, as preganglionic fibres come to impinge on cells previously innervated by other fibres. The process is comparable with that known to occur with sensory and motor fibres, and in the central nervous system, but seems to be more rapid and effective. It has important implications for any attempted autonomic denervation (bearing in mind the inaccessibility of the accessory ganglia), for sequelae of surgical sympathectomy such as gustatory sweating, for disease processes which produce partial denervations, and for certain classical phenomena such as the Sherrington, Phillipeaux-Vulpian, and Rogowicz pseudomotor reactions.

Conclusion

It is disappointing that, despite the advances made, we still cannot be confident in the specific identification of any central transmitter save acetylcholine. The processes by which the first sensory neurone transmits activity, or by which the motoneurone is excited or inhibited, let alone the other more complex excitations and inhibitions in higher centres, are still uncertain. Pharmacological study might be facilitated by using synapses with a large safety factor for transmission (on the assumption that a correspondingly vigorous release of transmitter would occur), by the discovery of ways of circumventing the blood-brain barrier, by further development of methods of administering, collecting, and assaying minute quantities of active substances, and by the more certain identification of the origins of some of the bioelectrical potentials studied. But the convergence of so much electrophysiological and pharmacological activity encourages hope that it will not be long before our knowledge of the chemistry of central transmission rises above its present tantalizingly subliminal level.

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